

## STN:Search History Report

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(FILE 'HOME' ENTERED AT 14:27:13 ON 19 JUN 2008)

FILE 'MEDLINE, SCISEARCH, CAPLUS, BIOSIS' ENTERED AT 14:27:40 ON 19 JUN 2008

L1 1 S CARDIAC (L) GENE THERAPY (L) CD9  
 L2 19 S GENE THERAPY (L) CD9  
 L3 8 DUP REM L2 (11 DUPLICATES REMOVED)

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L3 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2008 ACS on STN  
 TI Drug for preventing or treating heart diseases comprising CD9 gene  
 SO PCT Int. Appl., 45 pp.  
 CODEN: PIXXD2  
 IN Kosai, Kenichiro; Ushikoshi, Hiroaki  
 AB A drug for preventing or treating heart diseases which comprises an expression vector containing CD9 gene as the active ingredient. The term "heart diseases" as used above means diseases causative of heart failure, ischemic heart diseases, cardiomyopathy, hypertensive heart diseases, valvular disease, congenital heart diseases, myocarditis and diseases associated with arrhythmia, heart enlargement and/or frequent pulse. The above expression vector is a viral vector or a non-viral vector. A method of preventing or treating heart diseases which comprises expressing the CD9 gene in the heart. The prevention or the treatment is carried out by a gene therapy of transferring the CD9 gene. In the gene therapy, use is made of a drug comprising an expression vector containing the CD9 gene as the active ingredient.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005063302	A1	20050714	WO 2004-JP19774	20041224
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1716869	A1	20061102	EP 2004-808124	20041224
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				
US 20070161584	A1	20070712	US 2006-584109	20060622

L3 ANSWER 6 OF 8 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN  
 TI Membrane protein CD9 regulates hyperthrophy and heart failure via EGFR signaling in vitro and in vivo.  
 SO Circulation, (OCT 26 2004) Vol. 110, No. 17, Suppl. S, pp. 8.  
 Meeting Info.: 77th Scientific Meeting of the American-Heart-Association. New Orleans, LA, USA. November 07 -10, 2004. Amer Heart Assoc.

STN:Search History Report

CODEN: CIRCAZ. ISSN: 0009-7322.

AU Ushikoshi, Himaki [Reprint Author]; Takahashi, Tomoyuki; Esaki, Masayasu; Khai, Ngin C.; Kawai, Takao; Minatoguchi, Shinya; Fujiwara, Takako; Kosai, Ken-ichiro

AB Introduction: Cardiac hypertrophy is one of the important problems in cardiovascular diseases, because of causing heart failure. Heparin-binding EGF-like growth factor (HB-EGF) plays a large role in hypertrophic signaling and ischemia. On the other hand, prototype HB-EGF forms a complex with CD9, a cell membrane protein of the tetraspanin family. Hypothesis: We hypothesized that overexpression of CD9 on heart in vitro and in vivo by adenoviral gene transduction could regulate HB-EGF function, Methods: (1) In vitro experiments: Primary cultured mouse ventricular cardiomyocytes were infected with adenoviral vector expressing CD9 (Ad-CD9). Twenty-four hours later, these cells were stimulated by angiotensin 11 (TOO nmol/l) and recombinant HB-EGF (10 ng/ml). Cell volume, beating rates and EGFR signaling were evaluated. (2) In vivo experiments: A mouse ischemic heart failure model was generated by making myocardial infarction (MI) (permanent occlusion of coronary artery). Simultaneously, Ad-CD9, HB-EGF, CD9+HB-EGF, dE1.3 (each  $1 \times 10^{11}$  particle, each group  $n=14$ ) were directly injected into the heart. One week later, cardiac functions and histological changes were assessed. For survival rate and cardiac functions assessment, the mice were observed for eight weeks. Results: (1) Overexpression of CD9 inhibited hypertrophic effects (by angiotensin 11 and HB-EGF) on both cell volume and beating rates. Furthermore phosphorylation of mitogen-activated protein kinase and EGFR were decreased. (2) CD9 gene therapy reduced mortality in mice MI model. CD9 induction group improved cardiac function (LVEF; CD9:  $46.5 \pm 3.7\%$  VS control (dE1.3):  $32.3 \pm 5.1\%$ ,  $p<0.05$ ) and decreased heart weight (HW) in compared with control group (HW/Body weight; CD9:  $6.52 \pm 0.31$  VS dE1.3:  $8.40 \pm 0.56$ ,  $p<0.05$ ). On the other hand, only HB-EGF injection group induced left ventricular hypertrophy, and high mortality within two weeks. Histological findings showed inhibition of cardiomyocyte hypertrophy (CD9:  $13.3 \pm 1.88 \mu m$  vs dE1.3:  $18.1 \pm 1.55 \mu m$ ,  $p<0.01$ ) at the border area, and decreasing fibrosis area (CD9:  $15.5 \pm 3.7\%$  vs dE1.3:  $22.3 \pm 5.1\%$ ,  $p<0.05$ ). Conclusion: CD9 gene therapy could be a potent therapy for cardiac hypertrophy and ischemic heart failure via regulation of EGFR signaling.